

Multifocal nephrogenic adenoma treated by intravesical sodium hyaluronate

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Abstract

Nephrogenic adenoma is a rare benign urinary tract lesion. There are pediatric cases that have been managed with intravesical sodium hyaluronate, but there are no published adult cases. We present the first case of an adult successfully treated with intravesical sodium hyaluronate without resection. A 77-year-old man was investigated with cystoscopy for lower urinary tract symptoms (LUTS) unresponsive to medical therapy. This revealed multifocal flat black bladder lesions. Biopsy showed the lesions to be nephrogenic adenoma. His LUTS were treated with 6 weeks of intravesical sodium hyaluronate. He returned 6 weeks later for resection of his bladder lesions. However, resection was abandoned as the bladder lesions had entirely resolved. The resolution of the bladder lesions following intravesical sodium hyaluronate was unexpected but does agree with existing literature. The two reported pediatric cases also suggest that intravesical sodium hyaluronate is therapeutic for nephrogenic adenoma.

Keywords: Intravesical therapy, metaplasia, nephrogenic adenoma, sodium hyaluronate

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INTRODUCTION

Nephrogenic adenoma (also known as nephrogenic metaplasia, mesonephric adenoma, or adenomatoid metaplasia) is a rare benign urinary tract lesion. The etiology is under debate, but there is evidence to show that lesions can be formed by a process of seeding, implantation and growth of renal cells into urothelial mucosa.^[1] It is associated with chronic inflammation or irritation of the urinary tract and can be found in patients of all ages but most commonly in adults. The current opinion is that nephrogenic adenoma should be managed with transurethral resection, partial cystectomy, or diverticulectomy.^[2] There are case reports of pediatric patients who have been managed with intravesical sodium

hyaluronate after resection^[3,4] but none in adults. We present the first case of an adult who was successfully treated with intravesical sodium hyaluronate without resection.

CASE REPORT

A 77-year-old Caucasian male was referred with lower urinary tract symptoms (LUTS). His past medical history included insulin-dependent diabetes, chronic kidney disease, ischemic heart disease with previous coronary artery bypass, osteoarthritis, nephrolithiasis and benign prostatic hypertrophy. His nephrolithiasis consisted of a left proximal ureteric calculus and further left renal calculi; these had been managed by ureteric stenting and two flexible ureteroscopies with laser stone fragmentations

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4 years previously. His regular medication comprised finasteride, tamsulosin, solifenacin, aspirin, bisoprolol, omeprazole, simvastatin, fluoxetine, cholecalciferol with calcium carbonate, quinine, insulin and inhalers.

The symptoms he presented with were as follows: suprapubic discomfort, dysuria, frequency, nocturia 6–7 times per night, urgency and urge incontinence. He was initially investigated by computerized tomography of his urinary tract; this revealed calculi solely in the left kidney, the largest of which was a 12-mm lower pole calculus. He also underwent a flexible cystoscopy that showed bladder neck inflammation but otherwise normal mucosa. He was therefore managed with various anticholinergics and mirabegron with no symptomatic response. Given his failure to improve, the patient underwent urodynamics, these showed a small capacity bladder with stable detrusor on filling and equivocal pressures on voiding. Consequently, a cystoscopy and biopsy was organized to investigate for interstitial cystitis and to exclude carcinoma *in situ*.

The rigid cystoscopy revealed a normal urethra, a moderately occlusive prostate and multiple flat black lesions throughout the base of the bladder and up the lateral walls. There were also significant trabeculation and small developing diverticula. One of the black areas was biopsied with 2 samples taken for histological analysis. The area was then diathermied.

Macroscopically, the bladder biopsies were two fragments, the larger measuring 3 mm × 2 mm × 1 mm. Microscopy showed bladder mucosa including a lesion with tubulopapillary architecture. This comprised short papillae overlying closely packed hollow tubules, resembling mesonephric tubules, within the lamina propria. Some of these contained eosinophilic secretions. The papillae were covered by uniform cuboidal epithelial cells and tubules lined by cuboidal cells and hobnail cells. The cells had eosinophilic cytoplasm and round nuclei. Some degenerative atypia was identified, but there was no evidence of dysplasia, and no mitoses or necrosis was seen. There was marked associated mixed inflammation and hemosiderin-laden macrophages. Immunohistochemical staining showed positivity for Ca125, PAX8, CK7, and GATA3, with focal CK20 positivity, but no positive staining for P504S. The histological appearance and immunohistochemical profile were consistent with nephrogenic adenoma (metaplasia) of the bladder [Figures 1-3].

The patient was discussed at the local multidisciplinary meeting where the consensus was that he should have symptomatic management. He was offered both

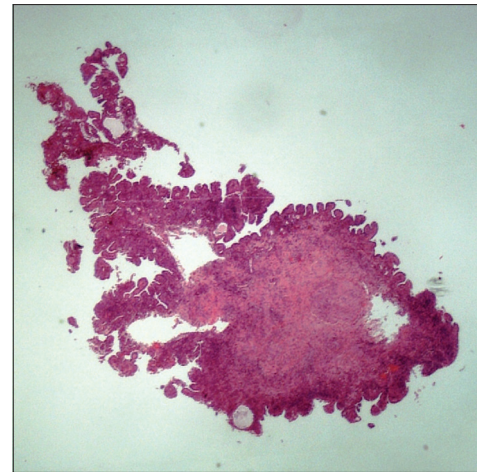


Figure 1: (Haematoxylin and Eosin, x2) this shows the predominant papillary architecture

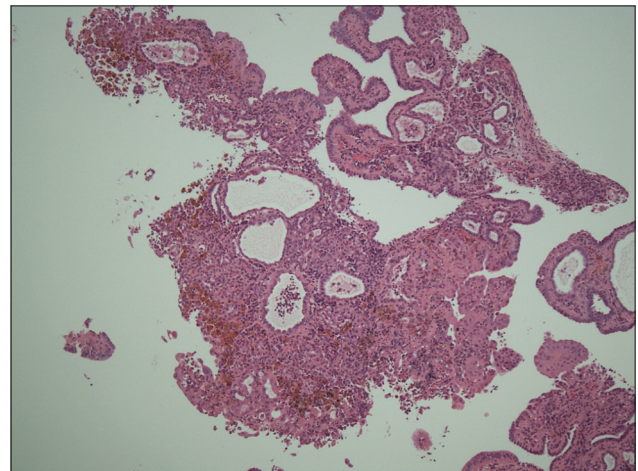


Figure 2: (Haematoxylin and Eosin, x10) this shows variably sized tubules in the lamina propria with associated hemosiderin-laden macrophages and mixed inflammatory cells

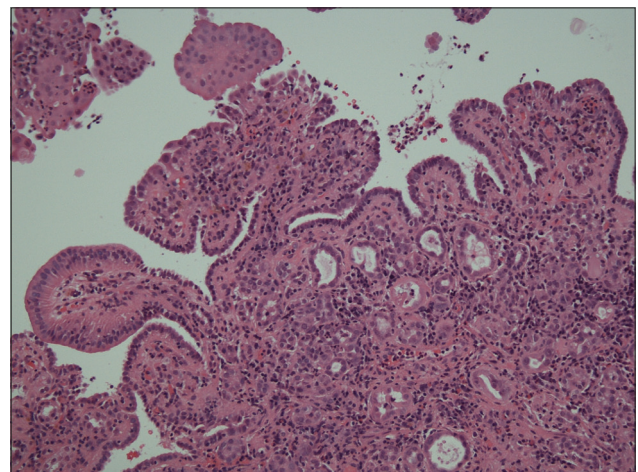


Figure 3: (Haematoxylin and Eosin, x20) this shows the bland cuboidal cells lining both the tubules and papillae

transurethral resection with diathermy or cystectomy and urinary diversion but was very adverse to the idea

of a cystectomy and so opted for transurethral resection. Before the resection, the patient was given a sheath to help his incontinence and commenced on weekly sodium hyaluronate (Cystistat® 40 mg/50 ml, Teva, UK) instillations for 6 weeks to help his LUTS. These were effective in significantly improving his suprapubic discomfort, dysuria, and nocturia. The patient attended for transurethral resection 6 weeks after his last sodium hyaluronate instillation. Cystoscopic evaluation of the bladder revealed 100-ml residual foul-smelling urine and mild inflammation of the bladder mucosa but complete resolution of the previously seen lesions and so no resection was performed.

DISCUSSION

Given that the recommended management of nephrogenic adenoma is surgical resection,^[2] the resolution of this patient's mucosal changes following intravesical sodium hyaluronate is unexpected.

There are two other reported cases of intravesical sodium hyaluronate being used in nephrogenic adenoma and both are in pediatric patients. One reports a 12-year-old boy with previous hypospadias repairs who presented with hematuria and stranguria and was found to have diffuse calculus-producing nephrogenic adenoma of the bladder. He is reported to have complete resolution following intravesical sodium hyaluronate instillations after resection, betamethasone, and anticholinergics failed.^[3] The other case is of a 7-year-old boy who had a ureteroneocystostomy for vesicoureteral reflux 5 years before his presentation with hematuria and severe dysuria. He was found to have multifocal exophytic tumors that were resected and found to be nephrogenic adenoma. He was then managed with a 3-month course of intravesical sodium hyaluronate and cystoscopic surveillance; he was found to have two small recurrences at year 4. The study does not report if there was any recurrence of symptoms or if the patient had any further intravesical treatment.^[4] Although in pediatric patients, these two cases confirm the positive relationship between intravesical sodium hyaluronate and the treatment of nephrogenic adenoma.

Further to existing literature, this case suggests that treating bladder inflammation alone may be sufficient to resolve nephrogenic adenoma of the bladder. This may be because

intravesical hyaluronic acid has been shown to reduce inflammatory cell infiltration and the severity of bladder inflammation^[5] which is known to be a predisposing factor for developing nephrogenic adenoma.^[2]

Given that intravesical hyaluronic acid has very few side effects^[6] compared to surgical resection, it would be reasonable to offer patients with nephrogenic adenoma a trial of intravesical sodium hyaluronate before further resection or cystectomy. However, since nephrogenic adenoma is rare, an organized trial is not feasible and further case reports will be required to provide further evidence on intravesical hyaluronic acid as a treatment option.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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